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10/525,736	06/06/2005	Amar Lulla	TPP 31757	8297

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EXAMINER	
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ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,736	LULLA ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *10-14 and 27-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/09/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1-33 are currently pending in the application.

Applicant's election with traverse to various groups and election of the preparation containing salmeterol, fluticasone, and tiotropium in the reply filed on 10/23/08 is acknowledged. The traversal is on the ground(s) that the prior art McNamara does not teach a combination of 2 or more active agents and consequently does not result in a lack of unity of invention. This is not persuasive given that McNamara clearly teaches the use of two or more active substances including budesonide, salbutamol, and tiotropium (see col.2, lines 28-55). As a result, these groups lack unity since no special technical features exist among the two groups and are patentably distinct and fully capable of supporting separate patents. Moreover, the search would indeed be unduly extensive and burdensome given that a search for these groups would consist of searching multiple databases for various references and literature searches.

Thus, the requirement is still deemed proper and is therefore made FINAL.

Claims 10-14 and 27-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group and species, there being no allowable generic or linking claim.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Provisional Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 8, 15-18, 20-22, and 24-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 9-10, and 12-13 of copending Application No. 11574902 (hereinafter Lulla US Patent Application No. '902) in view of Meade et al. (U.S. 2003/0018019 A1). Although the conflicting claims are not completely identical, they are not patentably distinct from each other because both applications are directed to a formulation comprising betamimetic such as salmeterol and anti-cholinergic such as tiotropium administered via inhalation or metered dose inhaler for the treatment of COPD.

While the co-pending application Lulla does not teach addition of corticosteroids, Meade et al. teach the combination of betamimetics such as salmeterol, anticholinergics such as tiotropium along with corticosteroids such as fluticasone for the treatment of COPD. Consequently, one of ordinary skill would have found it obvious to add corticosteroids to the composition of Lulla since Meade et al. teach their combination as effective in the treatment of COPD. Thus, the aforementioned claims of the instant application are substantially

overlapping in scope as discussed hereinabove and are prima facie obvious over the cited claims of corresponding application No. 11574902.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Scope of Enablement Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of certain respiratory conditions, does not reasonably provide enablement for all conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a pharmaceutical product comprising any one of the following combinations of therapeutic agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more of the therapeutic agents is indicated. The instant specification fails to provide information that would allow

the skilled artisan to practice the treatment of all conditions in existence or even all respiratory conditions.

[In re Sichert, 196 USPQ 209 (CCPA 1977)]

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a pharmaceutical product comprising any one of the following combinations of therapeutic agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more of the therapeutic agents is indicated. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites the fact that treatment of conditions utilizing corticosteroids, beta-mimetics and anti-cholinergic agents known in the art for certain respiratory conditions (i.e. COPD) but not for all conditions.

2. The breadth of the claims

The claims are thus very broad insofar as they recite the “treatment of all

conditions". While such "treatment" might theoretically be possible for some respiratory conditions, as a practical matter it is nearly impossible to achieve a treatment for all conditions (i.e. inclusive of cancer, diabetes, etc...) with the same compound.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for all conditions with the aforementioned compounds. No reasonably specific guidance is provided concerning useful therapeutic protocols for all conditions except for COPD. The latter is corroborated in the specification on page 1.

The instant disclosure provides no evidence to suggest that this unique activity can be extrapolated to rheumatoid arthritis, for example, having unrelated mechanisms of resistance, and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard thereto.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for the treatment of all

conditions as inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9 and 15-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Meade et al. (2003/0018019 A1).

Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Meade et al. teach novel pharmaceutical compositions based on anticholinergics, corticosteroids, and betamimetics (see abstract and pg. 1, paragraph 0001). Within the scope of the invention the term anticholinergics 1 denotes salts which are preferably selected from among tiotropium and most preferably tiotropium salts (see pg. 1, paragraph 0004). By salts, the present invention encompasses salts of tiotropium including the bromide salt wherein tiotropium bromide is particularly preferred (instant claims 1; see pg. 1, paragraphs 0004-0005). Within the scope of the invention, the word corticosteroids (hereinafter 2) denotes compounds selected from a group which includes fluticasone wherein the most preferred compounds including fluticasone (instant claims 1; see pg. 1, paragraphs 0006). Any reference to salts of corticosteroids include sodium salts, propionate salts, etc… (instant claim 2; see pg. 1, paragraph 0007). Examples of betamimetics (i.e. 3) which may be used in the present invention include preferred compound salmeterol or its salts including sulfate salts (instant claims 1; see pgs. 1-2, paragraphs 0008-0012). Meade et al. also teach that the three active substances are administered simultaneously in a single active substance formulation or administered successively in separate formulations (instant claim 1-4, 15-16, 20-21, and 24-25; see pg. 1, paragraph 0003). Additionally, Meade et al. teach that betamimetics 3 are optionally referred to as beta2-receptor agonists or ß2-agonists (see pg. 2, paragraph 0013). The pharmaceutical combination of 1, 2, and 3 (i.e. salmeterol, tiotropium and fluticasone; applicant's elected species; instant claims 1-4; pg. 3, paragraphs 0023-0025) are preferably administered by inhalation (instant claim 8) and

provided in the form of their enantiomers, mixtures of enantiomers or in the form of racemates, in the form of suitable inhalable powders (instant claims 18 and 22), or inhalation aerosols (instant claim 9, or as a solution (instant claim 23; see pg. 2, paragraphs 0014 and 0020-0022). Additionally, the present invention are administered in a therapeutic effective quantity and administered along with a pharmaceutically acceptable carrier (instant claim 3; see pg. 2, paragraph 0017-0018). The composition can be provided as inhalable powders (instant claim 18) and provided in admixture with excipients such as lactose (instant claims 3 and 19; pg. 5, paragraphs 0032-0035). Moreover, Meade et al. teach that the inhalable powders can be administered by means of metered dose inhalers (instant claim 17; see pg. 6, paragraph 0046 and pg. 7, paragraph 0055), using propellant free inhalable solutions or suspensions of the aforementioned combination (instant claim 23; see pg. 6, paragraphs 0047-0048 and pg. 9, paragraph 0088) or in nebulisers (instant claim 26; see pg. 7, paragraph 0056). Importantly, Meade et al. exemplify the inhalable powder containing tiotropium bromide in an amount of 0.0045% (i.e. anticholinergic %; instant claim 5), fluticasone propionate in an amount of 0.025% (i.e. corticosteroid; instant claim 7), and salmeterol xinafoate in an amount of 0.01% (i.e. B2-agonist; instant claim 6; see pg. 10, paragraphs 0097-0098).

Accordingly the teachings of Meade et al. anticipate claims 1-9 and 15-26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 15-22, and 24-26 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Keller et al. (U.S. 6,645,466 B1).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

It is respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention

from the prior art. If the prior art structure is capable of performing the intended use, then it meets the limitation of the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963). Thus, the intended use for the treatment of conditions is not afforded patentable weight.

Keller et al. teach enhanced dry powder formulations for inhalation which contain an ineffective pharmaceutical carrier and a finely divided pharmaceutically active compound (instant claims 8 and 22; see abstract and col. 4, lines 55-67). According to Keller, the active compounds in the formulation can be various compounds that can be administered by inhalation including a beta-mimetic such as salmeterol, an anti-cholinergic agent such as tiotropium, and a corticosteroid such as fluticasone, or a pharmaceutically acceptable derivative or salt thereof wherein the formulations can contain two or more of the aforementioned active compounds (instant claims 1, 3, 15, 20-21, and 24; see col. 6, lines 1-3 and 13-37). Additionally, Keller et al. teach the use of carriers such as lactose in multi-dose dry powder inhalers for improved flow properties and lubricating properties (see col. 3, lines 47-67). Salts or esters of the pharmaceutical compounds can be provided in the form a of salt including bromide, sulfate, propionate, etc…(instant claims 2, 4, 16, and 25; see col. 6, lines 40-50). Additionally, Keller et al. teach the use of magnesium stearate if the formulation contains a beta-mimetic such as salmeterol, and an anti-cholinergic

such as tiotropium bromide, and a corticosteroid such as fluticasone bromide (see col., lines 52-66). Additionally, the active compound can range approximately from 0.1%-10% by weight (instant claims 5-7; see col. 7, lines 11-22). All customary carriers used in dry powder inhalation can be used including mono and di-saccharides such as lactose (see col. 8, lines 1-4) and administered in a multi dose dry powder inhaler (col. 9, lines 21-27).

Keller et al. do not exemplify a formulation containing a beta-mimetic, an anti-cholinergic, and a corticosteroid. Similarly, Keller et al. does not teach the composition as an aerosol, in a nebuliser or a metered-dose inhaler.

Keller et al., however do teach that the formulations can contain two or more pharmaceutically active compounds (see col. 6, lines 13-37). Keller et al. further teach the use of magnesium stearate in dry powder formulations which contain a beta-mimetic, and/or an anti-cholinergic, and/or a corticosteroid or formulations in the form of the compounds' pharmaceutical salts such as salmeterol xinafoate, tiotropium bromide, and fluticasone propionate (applicant's elected species; see col. 6, lines 57-65).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to combine the active compounds disclosed by Keller et al. into a formulation since Keller et al. teach their use in dry powder formulations. Likewise, one of ordinary skill in the art at the time of the invention was made

would have found it obvious to formulate the composition as an aerosol, in a nebuliser or a metered dose inhaler for proper delivery of the composition. Moreover, one of ordinary skill would have found it obvious to substitute fluticasone for its salts (i.e. fluticasone propionate) given that the substitution of one known element for another would have yielded predictable results. Thus, given the teachings of Keller et al., one of ordinary skill would have been motivated to combine the beta-mimetic agent disclosed by Keller et al. with the anti-cholinergic agent, along with the corticosteroid and formulate the preparation in different forms since Keller et al. teach their use in dry powder inhalers for improved moisture resistance with the reasonable expectation of providing a formulation that is effective in moisture resistance.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

11/08/2008

/Shengjun Wang/

Primary Examiner, Art Unit 1617